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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,818	03/14/2002	Iqbal Grewal	146392002400	2744

25226 7590 08/08/2008

MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
08/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/099,818	GREWAL, IQBAL	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,14,15,19-33 and 36-55* is/are pending in the application.

4a) Of the above claim(s) *19 and 40-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-18,32,33,36-39 and 46-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/30/2008 has been entered.

Applicant's amendment, filed 04/30/2008, has been entered.

Claims 1, 14-15, 32-33, 37-39 and 46-49 have been amended.

Claims 50-55 have been added.

Claims 9-11, 13, 16-18 and 34-35 have been canceled.
Claims 12 and 20-31 have been canceled previously.

Claims 1-8, 14-15, 19-33 and 36-55 are pending.

The following of record is reiterated for applicant's convenience.

Newly submitted claims 40-45 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Newly submitted claims 40-45 are drawn to methods of further administering a cytotoxic or chemotherapeutic agent, including cytotoxic conjugates of CD40-specific / CD20-specific antibodies previously not claimed.

The newly submitted claims encompass the administration of cytotoxic or chemotherapeutic agents that differ in structure and function from the combination of anti-CD40 antibodies / anti-CD20 antibodies previously elected in the claimed methods of treating a neoplastic disease or disorder.

Further, the cytotoxic conjugates of CD40-specific / CD20-specific antibodies would differ from the previously elected CD40-specific / CD20-specific antibodies, including CD40-specific antibodies that stimulate CD40;

given that the modes of action of cytotoxic antibody conjugates would be expected to kill CD40-expressing neoplastic cells, rather than treating neoplastic diseases or disorders via the stimulation of CD40, as currently recited in the amended claims.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Given these differences between the newly submitted cytotoxic and chemotherapeutic agents, including cytotoxic antibody conjugates and the previous prosecution on methods employing CD40-specific antibodies and CD20-specific antibodies in the absence of cytoxotoxic and chemotherapeutic agents or cytotoxic antibody conjugates and the non-coextensive searches based upon such differences,

newly submitted claims 40-45 have been withdrawn from consideration as being drawn to the non-elected species based upon original presentation.

Further, it is noted that applicant has submitted these claims after a first Office Action after filing a RCE as well.

Applicant had the opportunity to submit these newly added limitations at the time the request for continued examination was filed.

Therefore, given the above, including issues under the various patent statutes and how they would apply to methods versus product claims; one or more of the following reasons apply, as indicated in the previous Office Action:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph

The newly submitted claims would be subject to election of species.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Accordingly, claims 19 and 40-45 have been withdrawn from consideration as being directed to a non-elected invention or species. See 37 C.F.R. 1.142(b) and M.P.E.P. 821.03.

As pointed out previously, applicant's election of Group I and the species of a CD40-specific antibody and a CD20-specific antibody as well as multiple myeloma in the reply filed on 11/14/2005 has been acknowledged.

Also, consistent with the previous indication, claims 1-11, 13-18, 32-33, 36-39 and 46-55 are under consideration in this application as they read on CD40-specific antibodies and CD20-specific antibodies as the specific agents as well as the various neoplastic diseases claimed in the interest of compact prosecution.

2. Objections:

Claim 5 is objected to because "non-hodgkins type lymphoma" should be non-Hodgkin's lymphoma".

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention

4. *This is a written description / new matter rejection.*

Claims 1-8, 14-15, 32-33, 36-39 and 46-55 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:

"derived from S2C6 (ATCC Accession No. PTA-110) and
"produced by the transfectoma having ATCC deposit number 69119".

Applicant relies upon the disclosure of the instant specification with respect to the anti-CD20 antibody rituximab (C2B8 antibody in U.S. Patent No. 5,736,137) and to the anti-CD40 S2C6 antibody for *these claimed biological materials.*

The following disclosure of the instant specification is noted with respect to the anti-CD20 antibody rituximab (C2B8 antibody in U.S. Patent No. 5,736,137) and to the anti-CD40 S2C6 antibody.

An anti-CD20 antibody, rituximab (RITUXAN.RTM. brand), is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen. Rituximab is the antibody called "C2B8" in U.S. Pat. No. 5,736,137 issued Apr. 7, 1998 (Anderson et al.). The antibody is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B cell non-Hodgkin's lymphoma. An open study of B-lymphocyte depletion through treatment with rituximab was conducted in rheumatoid arthritis patients the results suggesting that B-lymphocyte depletion maybe an effective therapy (Edwards and Cambridge (2001) Rheumatology 40:205-211). In vitro mechanism of action studies have demonstrated that the antibody binds human complement and lyses lymphoid B cell lines through complement-dependent cytotoxicity (CDC) (Reff et al. Blood 83(2):435-445 (1994)). Additionally, it has significant activity in assays for antibody-dependent cellular cytotoxicity (ADCC). More recently, it has been shown to have anti-proliferative effects in tritiated thymidine incorporation assays and to induce apoptosis directly, while other CD20 antibodies do not (Maloney et al. Blood 88(10):637a (1996)). Synergy between Rituximab and chemotherapies and toxins has also been observed experimentally. In particular, Rituximab sensitizes drug-resistant human B cell lymphoma cell lines to the cytotoxic effects of doxorubicin, CDDP, VP-16, diphtheria toxin and ricin (Demidem et al. Cancer Chemotherapy & Radiopharmaceuticals 12(3):177-186 (1997)). In vivo, preclinical studies have shown that it depletes B cells from the peripheral blood, lymph nodes, and bone marrow of cynomolgus monkeys, presumably through complement and cell-mediated processes (Reff et al. Blood 83(2):435-445 (1994)).

The humanized anti-CD20 antibody referred to as the "RITUXAN.RTM. brand" anti-CD20 antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen. Rituximab is the antibody called "C2B8" in U.S. Pat. No. 5,736,137 issued Apr. 7, 1998. The RITUXAN.RTM. brand of C2B8 antibody is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B cell non-Hodgkin's lymphoma.

CD20 specific agents included within the scope of the present invention include antibodies, synthetic or native sequence peptides and small molecule specific agents which bind to CD20, optionally conjugated with or fused to a cytotoxic agent. Preferred CD20 specific agents are antibodies directed against CD20 preferably monoclonal antibodies or fragments thereof. In aspects of the invention where the antibody binds to the CD20 surface antigen and causes depletion of the CD20 bearing cell types, binding is generally characterized by being capable of located and homing to the CD20 antigen bearing cell type in vivo. Suitable binding agents bind the CD20 antigen with sufficient affinity and/or avidity such that the CD20 specific agent is useful as a therapeutic agent for targeting a cell

expressing the antigen. Examples of antibodies which bind the CD20 antigen include: "C2B8" which is called "rituximab" (for example the "RITUXAN.RTM." brand) (U.S. Pat. No. 5,736,137, expressly incorporated herein by reference); the yttrium-[90]-labeled 2B8 murine antibody designated "Y2B8" (U.S. Pat. No. 5,736,137, expressly incorporated herein by reference); murine IgG2a "B1" optionally labeled with .sup.131I to generate the ".sup.131I-B1" antibody (BEXXAR.TM.) (U.S. Pat. No. 5,595,721, expressly incorporated herein by reference); murine monoclonal antibody "1F5S" (Press et al. Blood 69(2):584-591 (1987)); "chimeric 2H7" antibody (U.S. Pat. No. 5,677,180, expressly incorporated herein by reference); and monoclonal antibodies L27, G28-2, 93-1B3, B-C1 or NU-B2 available from the International Leukocyte Typing Workshop (Valentine et al., In: Leukocyte Typing III (McMichael, Ed., p. 440, Oxford University Press (1987)).

An exemplary humanized antibody of interest herein is based upon the sequence of murine antibody S2C6 which recognizes CD40 and is described in International Publication Number WO 00/75348 and comprises variable heavy domain complementarity determining residues GYSFTGYYIH, (SEQ ID NO: 1), RVIPNNGGTSYNQKFKG (SEQ ID NO:2) and/or EGI--YW (SEQ ID NO:3), and optionally comprises amino acid modifications of those CDR residues, e.g. where the modifications essentially maintain or improve affinity of the antibody. For example, the antibody variant of interest may have from about one to about seven or about five amino acid substitutions in the above variable heavy CDR sequences.

The humanized antibody may comprise variable light domain complementarity determining residues from murine S2C6 as well. Therefore, light chain CDR residues RSSQSLVHSNGNTFLH (SEQ ID NO:4), TVSNRFS(SEQ ID NO:5); and SQTTHVPWT (SEQ ID NO:6), e.g. in addition to those variable heavy domain CDR residues in the preceding paragraph are preferred. Such humanized antibodies optionally comprise amino acid modifications of the above CDR residues, e.g. where the modifications essentially maintain or improve affinity of the antibody. For example, the antibody variant of interest may have from about one to about seven amino acid substitutions in the above variable light CDR sequences.

In addition, applicant relies upon the following description of incorporation by reference in the specification as filed.

The following examples are offered by way of illustration and not by way of limitation. The disclosures of all citations in the specification are expressly incorporated herein by reference.

Applicant is reminded that to incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where the material is found in the various documents. See Advanced Display Systems, Inc. v. Kent State Univ., 54 USPQ2d 1673 (Fed. Cir. 2000) citing In re Seversky, 177 USPQ 144, 146 (CCPA 1973).

Also, see MPEP 608.01(p) for direction as to incorporation by reference of essential subject matter.

While the instant specification has provided disclosure of the anti-CD20 antibody rituximab and the anti-CD40 antibody S2C6;

there is insufficient identification with detailed particularity what specific material is being incorporated and where the material is found in the various documents with respect to written description as it reads on the claimed biological materials of *"ATCC Accession No. PTA-110) and the transfectoma having ATCC deposit number 69119"*.

Given the absence of the disclosure of the claimed biological materials of "ATCC Accession No. PTA-110) and the transfectoma having ATCC deposit number 69119" in the instant application and the insufficient identification with detailed particularity via incorporation by references of these claimed biological materials,

the recitation of the claimed biological materials of *"ATCC Accession No. PTA-110) and the transfectoma having ATCC deposit number 69119"* in the current claims changes the scope of the instant application.

Therefore, the instant specification as-filed does not provide a sufficient written description of of the claimed biological materials of *"ATCC Accession No. PTA-110) and the transfectoma having ATCC deposit number 69119"*.

The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Applicant is claiming a subgenus not supported by the specification as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action.

Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06

5. *This is a written description / not a new matter rejection.*

Claims 52-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite and encompass anti-CD40 antibodies which comprise less than six (6) CDRs or an entire variable heavy or light chain.

The recitation of claiming only three (3) CDRs do not meet the written description provision of 35 USC 112, first paragraph.

There is insufficient guidance and direction as to the written description of the claimed anti-CD40 antibodies.

Given the well known high level of polymorphism of immunoglobulins / antibodies, the skilled artisan would not have been in possession of the vast repertoire of antibodies and the unlimited number of antibodies encompassed by the claimed invention;
one of skill in the art would conclude that applicant was not in possession of the structural attributes of a representative number of species possessed by the members of the genus of anti-CD40 antibodies, broadly encompassed by the claimed invention.

One of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genera.

It has been well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. All of the heavy and light chain CDRs should be in their proper order and in the context of framework sequences which maintain their required conformation in order to provide a binding molecule having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79: 1979-1983 (1982).
Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.
Single amino changes to either a CDR or even in certain circumstances to the framework can result in decrease affinity of antigen or even ablation of antibody binding and specificity.

Also, see the teachings of Colman (Research in Immunology 145: 33-36, 1994) on the effects of amino acid sequence changes on antibody-antigen interactions.

In addition, Kussie et al. (J. Immunol. 152: 146-152, 1994) (e.g., see entire document, including Table I) teach that the substitution Of a single amino acid can totally ablate antigen binding.

Further, Chen et al. (EMBO J., 14: 2784-2794, 1995) teach that the substitution of a single amino acid can totally ablate antigen and that the same substitution in closely related antibodies can have opposite effects binding (e.g., see entire document, including Figure I). For example, the authors compared the effects of identical substitutions in related antibodies DI6 and TI5, and as shown in Figure 3, some substitutions increased antigen binding in one antibody while ablating it in the other.

However, the instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genera of "altered antibodies" and "modifying the sequence", broadly encompassed by the claimed invention.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

The problem here is that the instant specification fails to provide a disclosure of which residues are required for the antibody to have anti-CD40 binding specificities by claiming only three (3) CDRs, broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genus of S2C6-based anti-CD40 antibodies based upon only three (3) CDRs, broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is invited to recite all six (6) CDRs of the S2C6 antibody to obviate this rejection.

6. Upon reconsideration of applicant's amended claims, filed 04/30/2008, the previous rejection under U.S.C. § 102(e) as anticipated by Hanna et al. (US 2001/0018041 A1) (see entire document) and in further evidence of Armitage et al. (U.S. Patent No. 5,674,492 cited in paragraphs [0013] and [0104] of Hanna et al.), wherein said teachings of agonistic anti-CD40 are acknowledged by page 2, paragraph 1 of the instant specification and paragraphs [0005] and [0036] of Fanslow et al. (US 2005/0129689 A1) has been withdrawn.

7. Upon reconsideration of applicant's amended claims, filed 04/30/2008, the previous rejection under 35 U.S.C. § 103(a) as being unpatentable over Hanna et al. (US 2001/0018041 A1) in view of Siegall et al. (U.S. Patent No. 6,843,989) and Grillo-Lopez (U.S. Patent No. 6,455,043) and in further view of Armitage et al. (U.S. Patent No. 5,674,492 cited in paragraphs [0013] and [0104] of Hanna et al.) and Benoit et al. (Immunopharmacology 35: 129-139, 1996) (1449; #59), and in further evidence of the referenced teachings of agonistic anti-CD40 are acknowledged by page 2, paragraph 1 of the instant specification and paragraphs [0005] and [0036] of Fanslow et al., US 2005/0129689 A1) has been withdrawn.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. With respect to the previous obviousness rejection under 35 U.S.C. § 103(a), applicant's arguments, filed 04/30/2008, have been fully considered but have not been found convincing in view of the New Grounds of Rejection.

Although the prior art is nearly the same of record, the prior art have been constructed in such a fashion as to address applicant's arguments.

Applicant argues the following with respect to the previous obviousness rejection.

Although Hanna et al. state that the invention further contemplates combining anti-CD40L antibodies with anti-CD20 antibodies and/or anti-CD40 antibodies, this reference does not teach or suggest use of antibodies with characteristics of S2C6. See paragraph [0104] of Hanna et al. In addition, Example 3 of Hanna et al. showed that CD40L-CD40 signaling prevents apoptosis of B-lymphoma cells by anti-CD20 antibody RITUXAN®. See Table 1. The data in this Example indicates that activation of the CD40L-CD40 pathway by soluble CD40L (sCD40L) generated resistance of RITUXAN® induced apoptosis in DHL-4 lymphoma cells. In view of the data, one skilled in the art would be not be motivated to use an anti-CD40 antibody (such as antibody S2C6) that stimulates CD40 pathway in combination with an anti-CD20 antibody for treating a neoplastic disease or disorder. Therefore, data in Hanna et al. teaches away from use of an agent that stimulates CD40 in combination with an anti-CD20 antibody for treating a neoplastic disease or disorder.

Benoit et al. do not provide further motivation to combine a chimeric antibody or a humanized antibody derived from S2C6 with an anti-CD20 antibody in the treatment of a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal. Benoit et al. discloses increased inhibition of proliferation of human B cell lymphomas following ligation of CD40 and CD20. The experiment described in this reference is based on use of anti-CD40 antibody produced by hybridoma G28.5. Benoit et al. do not disclose any other characteristics of this antibody besides it binds to CD40 and inhibits growth of certain B lymphoma cells. As indicated in Siegall et al., different anti-CD40 antibodies have different characteristics, such as on promoting CD40/CD40L interactions. See WO 00/75347, pages 52 to 56, sections 7.1.4, 7.1.5, 7.2.1, and 7.2.2. For example, data in Siegall et al. showed antibody S2C6 enhanced CD40/CD40L interaction in in vitro studies; in contrast, antibody G28-5 and antibody M3 inhibited the interaction between CD40 and CD40L. See WO 00/75347, page 54, line 1 to page 55, line 16. Accordingly, one skilled in the art would not view that the teachings in Benoit et al. could be applied to antibody S2C6.

Furthermore, none of Siegall et al., Grillo-Lopez, Armitage et al., and Fanslow et al. teach or provides the motivation to use an anti-CD20 antibody with a chimeric antibody or a humanized antibody derived from antibody S2C6 for treating a neoplastic disease or disorder as claimed. In view of the above, one skilled in the art would not be motivated to administering an anti-CD20 antibody with a chimeric antibody or a humanized antibody derived from antibody S2C6 for treating a neoplastic disease or disorder as claimed.

In addition, Applicant respectfully submits that there is no reasonable expectation of success. As discussed above, data in Hanna et al. indicates that CD40L-CD40 signaling prevents apoptosis of B-lymphoma cells by anti-CD20 antibody, RITUXAN®. In view of this teaching, one skilled in the art would not expect an anti-CD40 antibody that stimulates CD40 and enhances the interaction between CD40 and CD40L (such as S2C6) in combination with an anti-CD20 antibody would have a better effect in treating B-lymphoma as compared to use of each antibody alone. Benoit et al. only disclose use of a specific antibody G28.5 under crosslinking conditions, and Siegall et al. showed antibody G28-5 and antibody M3 inhibited the interaction between CD40 and CD40L, in contrast to the antibody S2C6 which enhanced CD40/CD40L interaction in in vitro studies. In view of the teachings in these references, one skilled in the art would not reasonably expect that an anti-CD40 antibody having characteristics of S2C6 in combination with an anti-CD20 antibody would have more than a cumulative effect in treating a neoplastic disorder or disease.

In addition, Applicant respectfully submits that specification shows that the anti-CD20 antibody used in combination with anti-CD40 antibody S2C6 have more than cumulative effect in antitumor activity. Example I of the present application is based on the experiments using anti-CD40 antibody S2C6 and anti-CD20 antibody RITUXAN®. The data in Example I shows that "[s]urvival was extended in mice receiving a combination of anti-CD40 antibody and anti-CD20 antibody compared with control animals and animals receiving anti-CD40 antibody or anti-CD20 antibody alone." See Specification at page 46, lines 22 -25. This result was not merely a cumulative effect based upon the use of the anti-CD40 antibody and the anti-CD20 antibody. As shown in Figure 4, three out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the anti-CD40 antibody while five out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the anti-CD20 antibody.

In contrast, ten out of twelve mice survived 150 days post tumor (multiple myeloma) implantation with treatment using the combination of the anti-CD20 antibody and the anti-CD40 antibody. See Figure 4. Further, the "[t]umor volume in mice receiving a combination of anti-CD40 antibody and anti-CD20 antibody was significantly reduced compared to control animals and animals receiving anti-C40 antibody or anti-CD20 antibody alone." See Specification at page 46, lines 29-33. As shown in Figure 5, one out of ten mice treated with the anti-CD40 antibody alone were tumor free (Ramos lymphoma) while ten out of ten mice treated with the combination of the anti-CD40 antibody and the anti-CD20 antibody were tumor free (Ramos lymphoma). In view of the references cited by the Examiner, this non-cumulative effect shown in Example I was surprising and unexpected.

In view of the above, Applicant respectfully submits that the Examiner has not established a prima facie case of obviousness, and claims as amended are not obvious over the references cited by the Examiner. Applicant respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Given that Hanna et al. is not the primary reference of the current obviousness rejection set forth herein, applicant's arguments have not been found persuasive.

10. Claims 1-8, 14-15, 32-33, 36-39 and 46-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Siegall et al. (U.S. Patent No. 6,843,989) (892; of record) in view of Li et al. (U.S. Patent No. 6,495,129), Hanna et al. (US 2001/0018041 A1) and Grillo-Lopez (U.S. Patent No. 6,455,043) (892; of record), Benoit et al. (Immunopharmacology 35: 129-139, 1996) (1449; #59).

Siegall teach methods of treating cancer, including leukemias, lymphomas (e.g. non-Hodgkins lymphoma), solid tumor and multiple myeloma (e.g. see Therapeutic Uses, including Table 1 on columns 22-23 and Claims) with CD40-specific antibodies, including the S2C6 CD40-specific antibody of the instant invention (see entire document, including Claims)

Siegall differs from the claimed methods by not disclosing the known use of combination therapy in the treatment of neoplastic diseases or disorders, including the use of anti-CD20 antibodies in the treatment of such neoplastic diseases or disorders.

Li et al. teach the well known use of combination therapy in the treatment of such neoplastic diseases or disorders (e.g., columns 86-),
including leukemias, lymphomas and multiple myeloma as the elected species (e.g., columns 102 and column 151),
including Rituximab / anti-CD20 antibodies (see column 147, paragraph 3)
and anti-CD40 antibodies, including agonistic antibodies (e.g., see column 3, paragraph 3)

Grillo-Lopez teach treating various tumors with CD20-specific antibodies, including Rituixmab (see columns 5-8 (see entire document) and teachings the expression of CD20 on multiple myeloma (e.g. see columns 15-16, overlapping paragraph) in addition to leukemias and lymphomas (e.g. see Field of the Invention on column 1 and Detailed Description of the Invention and Claims).

Benoit et al. provides additional motivation of combining anti-CD40 antibodies with anti-CD20 antibodies in the treatment of B cell lymphomas.

Benoit et al. teach the increased inhibition of proliferation of B cell lymphomas following litigation of CD40, and CD20, for example (see entire document, including Abstact and Discussion).

Given both the therapeutic use of CD40-specific antibodies and CD20-specific antibodies to treat various neoplastic diseases, including leukemias, lymphomas, myelomas and solid tumors, the ordinary artisan would have been motivated to combine the two antibody specificities in combination therapies to target other neoplastic tissues in order to increase the efficacy of cancer treatment. As taught by all of the prior art references, combination therapies, including combination with antibodies or combination of antibodies with more traditional chemotherapy and radiotherapy were well known and practiced by the ordinary artisan at the time the invention was made to increase efficacy of treatment and to minimize toxic effects of such treatment in order to meet the needs of the patients (e.g., see Detailed Descriptions of Siegall and Grillo-Lopez). The claimed recombinant antibodies and antigen-binding fragments were well known and employed at the time the invention was made. Modes of administration (e.g. simultaneously and sequentially) were practiced by the ordinary artisan as standard regimens in meeting the needs of the patient at the time the invention was made.

In this case the teachings of the prior art do provide for the use of anti-CD40 antibodies in the treatment of certain neoplastic disorders and diseases and do indicate success in treating neoplastic disorders and diseases with anti-CD40 antibodies in combination with anti-CD20 antibodies that would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the combination of the prior art disclosure in motivating the ordinary artisan to administer anti-CD20 antibodies and anti-CD40 antibodies to treat patients with neoplastic diseases or conditions.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to treat patients with neoplastic diseases or conditions with anti-CD20 antibodies and anti-CD40 antibodies,
incorporating the combination of anti-CD20 antibodies and anti-CD40 antibodies in therapeutic regimens with patients with neoplastic diseases or disorders would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such therapeutic methods to treat said neoplastic diseases and disorders.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-8, 14-15, 32-33, 36-39 and 46-55 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-18 and 31-53 of copending USSN 11/537,559.

The instant and copending claims appear to be drawn to the same or nearly the same methods of treating neoplastic diseases or disorders (including non-elected species) with the same or nearly the same CD40-specific antibodies and CD20-specific antibodies. Therefore, the copending claims and the instant claims appear to anticipate or render obvious one another.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phillip Gambel/

Phillip Gambel, Ph.D., J.D.
Primary Examiner
Technology Center 1600
Art Unit 1644
August 4, 2008